



الهيئة السعودية للتخصصات الصحية  
Saudi Commission for Health Specialties

# Direct Oral Anticoagulants Clinical Pathway



EDITION YEAR

**OCTOBER 2020**



الهيئة السعودية للتخصصات الصحية  
Saudi Commission for Health Specialties

## CONTRIBUTORS

October 2020, Edition Number: 01

### Preparation Scientific Group

Dr. Hala M. Alkhalidi

### Reviewed by

Dr. Ahmad Aljedai

### Supervision

Dr. Abdullah Alkhenizan

### Review and Approval

- Council of Corporative Health Insurance
- Professional Council of Physicians
- Saudi Society of Clinical Pharmacy
- Supervision Council of Health Association



Saudi Society of Clinical Pharmacy  
الجمعية السعودية للصيدلة الإكلينيكية



الهيئة السعودية للتخصصات الصحية  
Saudi Commission for Health Specialties



All rights reserved. Copyright © 2020 Saudi Commission for Health Specialties

This material may not be reproduced, displayed, modified, or distributed without the prior written permission of the copyright holder

No other use is permitted without the prior written permission of the Saudi Commission for Health Specialties

For permission to reproduce this material, contact the Saudi Commission for Health Specialties, Riyadh, Kingdom of Saudi Arabia

## CORRESPONDENCE

P.O. Box: 94656

Postal Code: 11614

Consolidated Communication Center: 920019393

International Contact Number: 00-966-114179900

Fax: 4800800

PSHA@SCFHS.ORG

Website: [www.scfhs.org.sa](http://www.scfhs.org.sa)



### Disclaimer

The information included in this document has been adapted and compiled from various international sources and guidelines.



الهيئة السعودية للتخصصات الصحية  
Saudi Commission for Health Specialties



Sl. no	Topics	Page No.
1	List of Tables and Figures	05
2	Abbreviations	06
3	Introduction <ul style="list-style-type: none"> <li>a) AHFS therapeutic class</li> <li>b) Targeted audience</li> <li>c) Inclusion criteria</li> <li>d) Exclusion criteria</li> </ul>	07
4	Methodology	08
5	Approved Indications and Dosing For Normal Renal and Hepatic Function	09
6	Use of DOACs in Venous Thromboembolism Clinical Pathway	10
7	Use of DOACs in Nonvalvular Atrial Fibrillation Clinical Pathway	11
8	Use of DOACs in Special Population <ul style="list-style-type: none"> <li>a) Use of DOACs in renal impairment</li> <li>b) Use of DOACs in hepatic impairment</li> </ul>	12
9	Drug-Drug Interactions	13
10	Monitoring	14
11	Perioperative Management of DOACs Clinical Pathway	15
12	Management of Bleeding in Patients Taking DOACs	16
13	Transitioning Between Anticoagulants	17
14	References	18
15	Appendix	19



Sl. no	Topics	Page No.
<b>1</b>	<b>Main List of Tables:</b>	
	a) Table I: Approved Indications and Dosing For Normal Renal and Hepatic Functions _____	<b>09</b>
	b) Table II: Use of DOACs in Renal Impairment (As Determined by Cockcroft-Gault Equation*) _____	<b>12</b>
	c) Table III: Use of DOACs in Hepatic Impairment (Based on Child-Pugh Score for Classification of Hepatic Impairment; Appendix III) _____	<b>12</b>
	d) Table IV: Drug-Drug Interactions _____	<b>13</b>
	e) Table V: Perioperative Management of DOAC Clinical Pathway _____	<b>15</b>
<b>2</b>	<b>Main List of Figures:</b>	
	a) Pathway I: Use of DOACs in Venous Thromboembolism Clinical Pathway _____	<b>10</b>
	b) Pathway II: Use of DOACs in Nonvalvular Atrial Fibrillation Clinical Pathway _____	<b>11</b>
	c) Pathway III: DOAC Monitoring Parameters _____	<b>14</b>
	d) Pathway IV: Management of Bleeding in Patients Taking DOACs _____	<b>16</b>
	e) Pathway V: Transitioning Between Anticoagulants _____	<b>17</b>
<b>3</b>	<b>Appendix List of Tables:</b>	
	a) Table I: CHA2DS2-VASc Score _____	<b>19</b>
	b) Table II: HAS-BLED Score _____	<b>20</b>
	c) Table III: Child-Pugh Score for Classification of Hepatic Impairment _____	<b>21</b>



## Sl. no

<b>1</b>	<b>ACS</b>	Acute coronary syndrome
<b>2</b>	<b>AF</b>	Atrial fibrillation
<b>3</b>	<b>APS</b>	Antiphospholipid syndrome
<b>4</b>	<b>ESRD</b>	End stage renal disease
<b>5</b>	<b>FXa</b>	Factor Xa
<b>6</b>	<b>OACs</b>	Oral anticoagulants
<b>7</b>	<b>P-gp</b>	P-glycoprotein
<b>8</b>	<b>VTE</b>	Venous thromboembolism
<b>9</b>	<b>CYP</b>	Cytochrome P450
<b>10</b>	<b>PCC</b>	Factor IX complex, made up of clotting factors II, IX, and X
<b>11</b>	<b>SE</b>	Systemic embolism
<b>12</b>	<b>TT</b>	Thrombin time
<b>13</b>	<b>NG</b>	Nasogastric
<b>14</b>	<b>GT</b>	Gastrostomy

## Disclaimer

The following recommendations should be used as clinical guidance and does not override the clinical judgment of healthcare professionals. The provided recommendations were made based on the best available evidence and are subject to change.



**a) AHFS therapeutic classes:**

- Rivaroxaban; apixaban; edoxaban: 20:12.04.14 direct factor Xa inhibitors
- Dabigatran: 20:12.04.12 direct thrombin inhibitors

**b) Targeted audience:**

Physicians in primary, secondary, and tertiary care hospitals, clinical pharmacists, and nurses

**c) Inclusion criteria:**

- Adult patients  $\geq 18$  years
- Without valvular atrial fibrillation (AF)  
(i.e., AF with moderate-to-severe mitral stenosis and/or mechanical heart valve)

**d) Exclusion criteria:**

- Pediatric patients  $< 18$  years
- Patients with valvular AF
- Patients with antiphospholipid syndrome (APS)
- Patients with active cancer



The ADAPTE process was used, modified to Five Steps as developed by Kristiansen et al, which include:



Multiple workshops were conducted over a one-year duration (2019-2020). The Five Steps adaptation process was selected because of its simple and practical approach. The final document was peer-reviewed and edited accordingly.



**Table I: Approved Indications and Dosing For Normal Renal and Hepatic Functions**

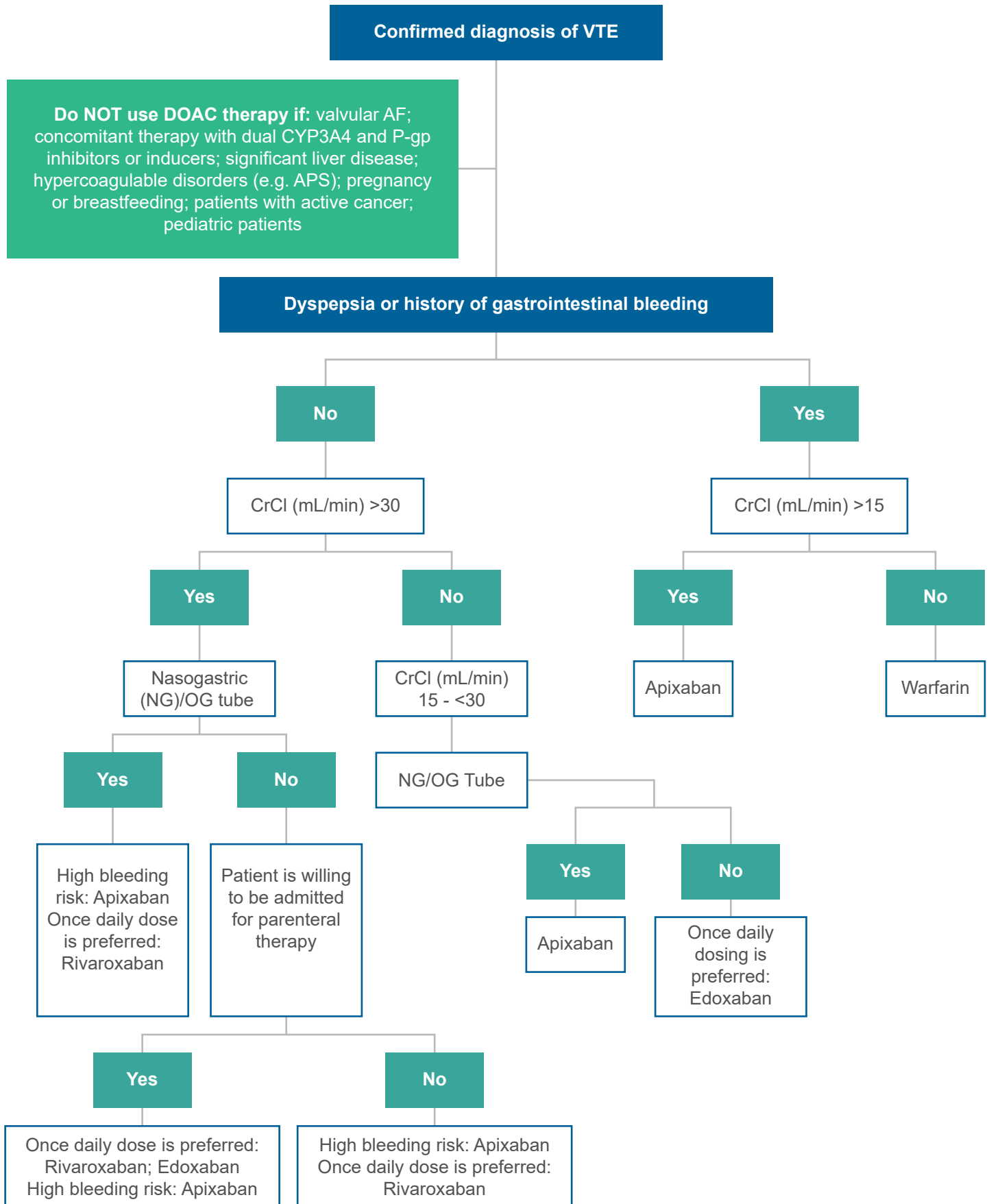
Indication	Rivaroxaban	Apixaban	Edoxaban <sup>h</sup>	Dabigatran
Nonvalvular atrial fibrillation <sup>a</sup>	20 mg daily	5 mg twice daily <sup>g</sup>	60 mg daily	150 mg twice daily
Treatment of venous thromboembolism (VTE) <sup>b</sup>	15 twice daily for 21 days; then 20 mg daily	10 mg twice daily for 7 days followed by 5 mg twice daily	≤60 kg: 30 mg daily <sup>i</sup> >60 kg: 60 mg daily <sup>i</sup>	150 mg twice daily <sup>i</sup>
Indefinite anticoagulation <sup>c</sup>	10 mg daily			
Coronary artery disease (stable) or peripheral artery disease <sup>d</sup>	2.5 mg twice daily			
VTE prophylaxis in acutely ill medical patients	10 mg daily for 31 to 39 days <sup>f</sup>			
VTE prophylaxis in total hip or knee arthroplasty <sup>e</sup>	10 mg daily	2.5 twice daily		220 mg daily <sup>j</sup>

■ Approved    ■ Unapproved

- a To reduce the risk of stroke and systemic embolism in patients with AF without moderate-to-severe mitral stenosis and/or mechanical heart valve
- b Deep vein thrombosis and/or pulmonary embolism to reduce risk of VTE following initiation of therapy
- c Reduced intensity of dosing against VTE recurrence for patients at an elevated risk of recurrent VTE after 6 or more months of therapeutic anticoagulation. Not recommended if indefinite full anticoagulant therapy is indicated
- d In select patients with a high risk of cardiovascular events and low risk of bleeding if dual antiplatelet therapy or therapeutic anticoagulation is not indicated for other indications
- e Initiated ≥6 to 10 hours after surgery or when hemostasis is established. For 10 to 14 days for total knee arthroplasty and for 35 days for total hip arthroplasty
- f Including hospitalization and post-discharge
- g Reduce to 2.5 mg twice daily if age ≥80 years and body weight ≤60 kg
- h Do not use if CrCl >95 mL/min (Cockcroft-Gault equation)
- i After at least 5 days of initial therapy with a parenteral anticoagulant, transition to edoxaban or dabigatran in hemodynamically stable patients
- j 110 mg administered 1–4 hours after surgery completion and hemostasis establishment or when dabigatran is not initiated on the day of surgery, administer an initial dose of 220 mg after achieving hemostasis; then continue a maintenance dose of 220 mg once daily

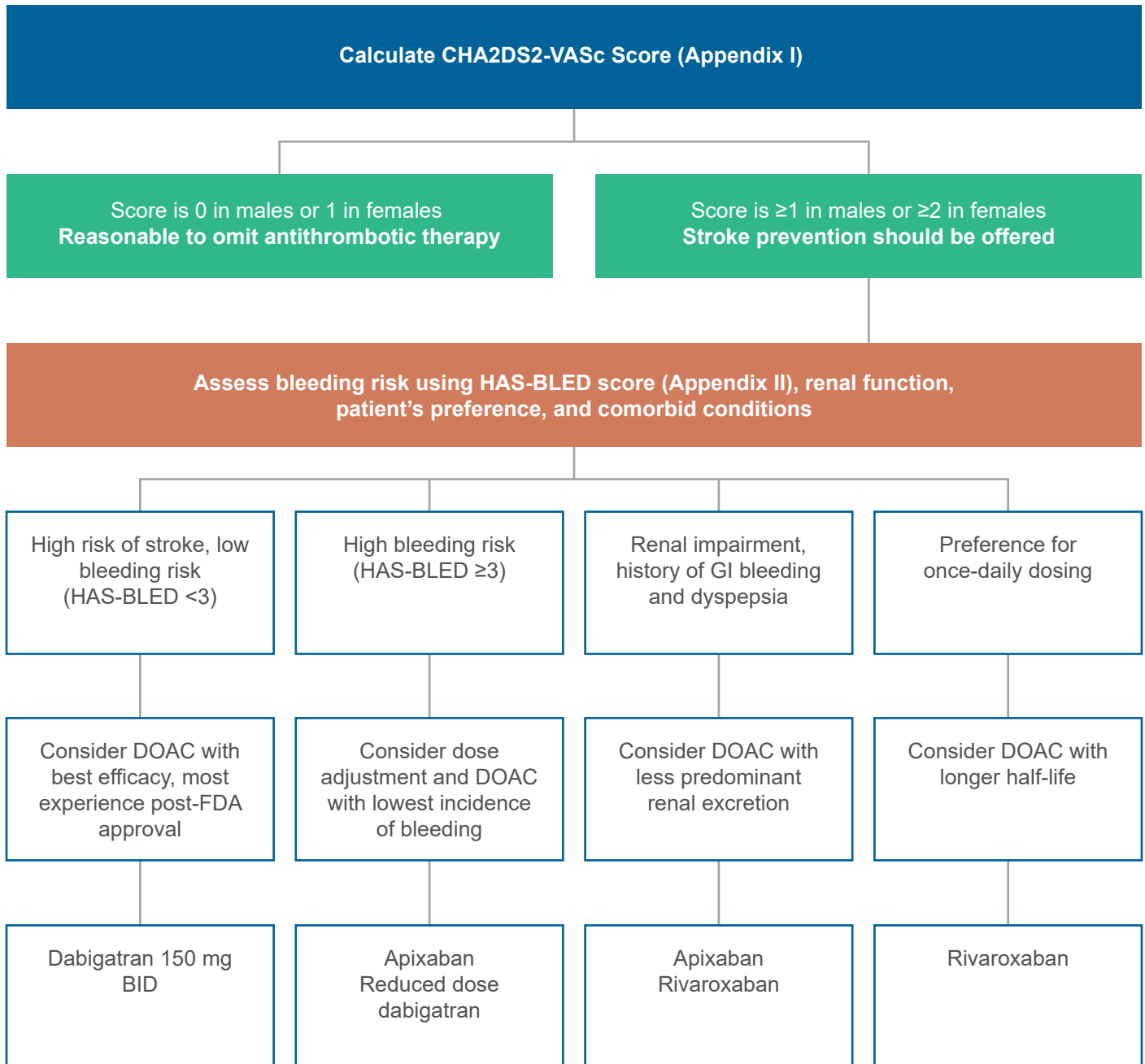


## Pathway I: Use of DOACs in Venous Thromboembolism Clinical Pathway





## Pathway II: Use of DOACs in Nonvalvular Atrial Fibrillation Clinical Pathway



Source: J Thorac Dis 2015;7:115-31

For dosing, please refer to Tables I, II, or III



**Table II: Use of DOACs in Renal Impairment (As Determined by Cockcroft-Gault Equation\*)**

CrCl (mL/min)	Rivaroxaban		Apixaban <sup>b</sup>	Edoxaban	Dabigatran			
>95	No dosage adjustment	No dosage adjustment	No dosage adjustment	Avoid use	No dosage adjustment			
>50				No dosage adjustment				
30 to 50	AF: 15 mg daily	VTE <sup>a</sup>		30 mg daily				
15 to <30		VTE <sup>a</sup>					AF: 75 mg twice daily	VTE
<15	Avoid use			Avoid use			Avoid use	
End-stage renal disease	Avoid use			2.5 to 5 mg twice daily			Avoid use	

■ No dosage adjustment    
 ■ Dosage adjustment is needed    
 ■ Avoid use    
 ■ Limited data available

\* Creatinine clearance =  $\{((40 - \text{age}) \times \text{weight}) / (72 \times \text{SCr})\} \times 0.85$  (if female)

a Contraindicated for VTE treatment, reduced intensity for VTE recurrence, or prophylaxis for medically ill patients or after total hip or knee arthroplasty

b Reduce apixaban dose to 2.5 mg twice daily in patients with AF if serum creatinine  $\geq 1.5$  mg/dL (133  $\mu\text{mol/L}$ ) and either  $\geq 80$  years or body weight  $\leq 60$  kg

**Table III: Use of DOACs in Hepatic Impairment (Based on Child-Pugh Score for Classification of Hepatic Impairment; Appendix III)**

Child-Pugh Score	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
A	No dosage adjustment	No dosage adjustment	No dosage adjustment	No dosage adjustment
B	Contraidicted	Use with caution	Use with caution	Use with caution
C		Contraidicted	Contraidicted	Contraidicted

■ No dosage adjustment    
 ■ Use with caution    
 ■ Contraidicted



**Table IV: Drug-Drug Interactions**

Agent	Drug Interaction	Effect of DOAC	Recommendations
Dabigatran	P-gp inhibitors	Increase in concentration	Reduce dose or avoid depending on renal function
	P-gp inducers	Significant reduction in concentration	Avoid use
	Antacids	Moderate reduction in concentration	No dose adjustments required; consider spacing regimens by 2 hours
Apixaban	Strong CYP3A4 inhibitor + P-gp inhibitor	Significant increase in concentration	Reduce dose or avoid use
	Moderate CYP3A4 inhibitor + P-gp inhibitor	Moderate increase in concentration	No dose adjustments required; use with caution Avoid use in patient with severe renal insufficiency
	Strong CYP3A4 inducer or P-gp inducer	Significant reduction concentration	Avoid use
Rivaroxaban	Strong CYP3A4 inhibitor + P-gp inhibitor	Significant increase in concentration	Avoid use
	Moderate CYP3A4 inhibitor + P-gp inhibitor	Moderate increase in concentration	No precaution necessary Avoid use in patient with severe renal insufficiency
	Strong CYP3A4 inducer or P-gp inducer	Significant reduction concentration	Avoid use
Edoxaban	P-gp inhibitors	Increase in concentration	AF: Do not reduce dose VTE treatment: Reduce dose
	P-gp inducers	Significant reduction in concentration	Avoid use with rifampin
<b>Drug Interaction Examples</b>			
Strong CYP3A4 inhibitors + combined P-gp inhibitor		Itraconazole, ketoconazole, ritonavir	
Moderate CYP3A4 inhibitors + combined P-gp inhibitor		Clarithromycin, diltiazem	
Strong CYP3A4 inducer + combined P-gp inducer		Carbamazepine, rifampin, St. John's wort	
Strong CYP3A4 inducers		Phenytoin	
P-gp inhibitors		Amiodarone, clarithromycin, cyclosporine, dronedarone, erythromycin, ivacaftor, ketoconazole, nifedipine, quinidine, ranolazine, ticagrelor, tolvaptan, verapamil	
P-gp inducers		Rifampin	

Source: American Heart Association, Inc.



## Pathway III: DOAC Monitoring Parameters

### Baseline

- Assess the need of therapy
- Assess bleeding risk
- Assess adherence
- Renal function, complete blood count (CBC), hepatic function
- Assess co-medications
- Start a DOAC at the right dose
- Provide education
- Arrange for follow-up appointment

### After 3-6 months


- Check for bleeding/thromboembolic events
- Assess adherence
- Renal function, CBC, hepatic function
- Assess co-medications
- Assess optimal and correct dosing
- Arrange for follow-up appointment

### Annually or when necessary

- Check for bleeding/thromboembolic events
- Assess adherence
- Renal function, CBC, hepatic function
- Assess co-medications
- Assess optimal and correct dosing
- Arrange for follow-up appointment



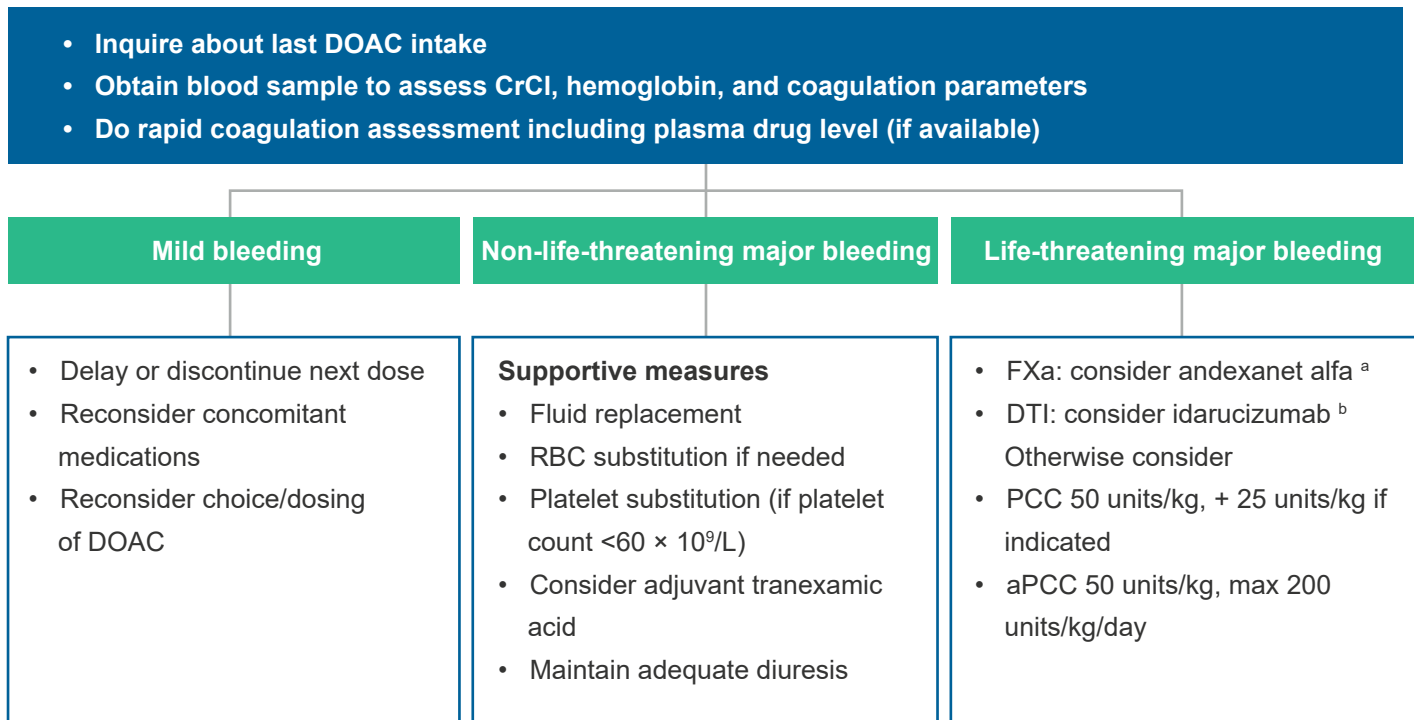
**Table V: Perioperative Management of DOAC Clinical Pathway**

	 <b>Cockcroft-Gault creatinine clearance</b>				
<b>Procedure bleeding risk</b>	≥80 mL/min	≤50–79 mL/min	≤30–49 mL/min	≤15–29 mL/min	≤15 mL/min
<b>Minor-bleeding risk procedure</b>	<ul style="list-style-type: none"> <li>Recommended not to stop in most minor surgical procedures</li> <li>Stop: 12–24 h before procedure*</li> <li>Restart: 6 h after intervention</li> </ul>				
<b>Low-bleeding risk procedure</b>	DTI: STOP ≥24 h FXa: STOP ≥24 h	DTI: STOP ≥36 h FXa: STOP ≥24 h	DTI: STOP ≥48 h FXa: STOP ≥24 h	DTI: Not indicated FXa: STOP ≥36 h	Not indicated
<b>High-bleeding risk procedure</b>	DTI: STOP ≥48 h FXa: STOP ≥48 h	DTI: STOP ≥72 h FXa: STOP ≥48 h	DTI: STOP ≥96 h FXa: STOP ≥48 h	DTI: Not indicated FXa: STOP ≥48 h	Not indicated

- Minor-bleeding-risk interventions: dental, cataract, glaucoma, endoscopy without biopsy or resection, superficial surgery
- Low-bleeding-risk interventions: endoscopy with biopsy, prostate biopsy, bladder biopsy, pacemaker or implantable cardioverter-defibrillator implantation, noncoronary angiography, electrophysiological study/catheter ablation
- High-bleeding-risk interventions: major surgery, spinal puncture or placement of spinal/epidural catheter, other situations in which complete hemostasis is required
- \*Skip 1 dose of dabigatran or apixaban; no dose of edoxaban or rivaroxaban is skipped



## Pathway IV: Management of Bleeding in Patients Taking DOACs



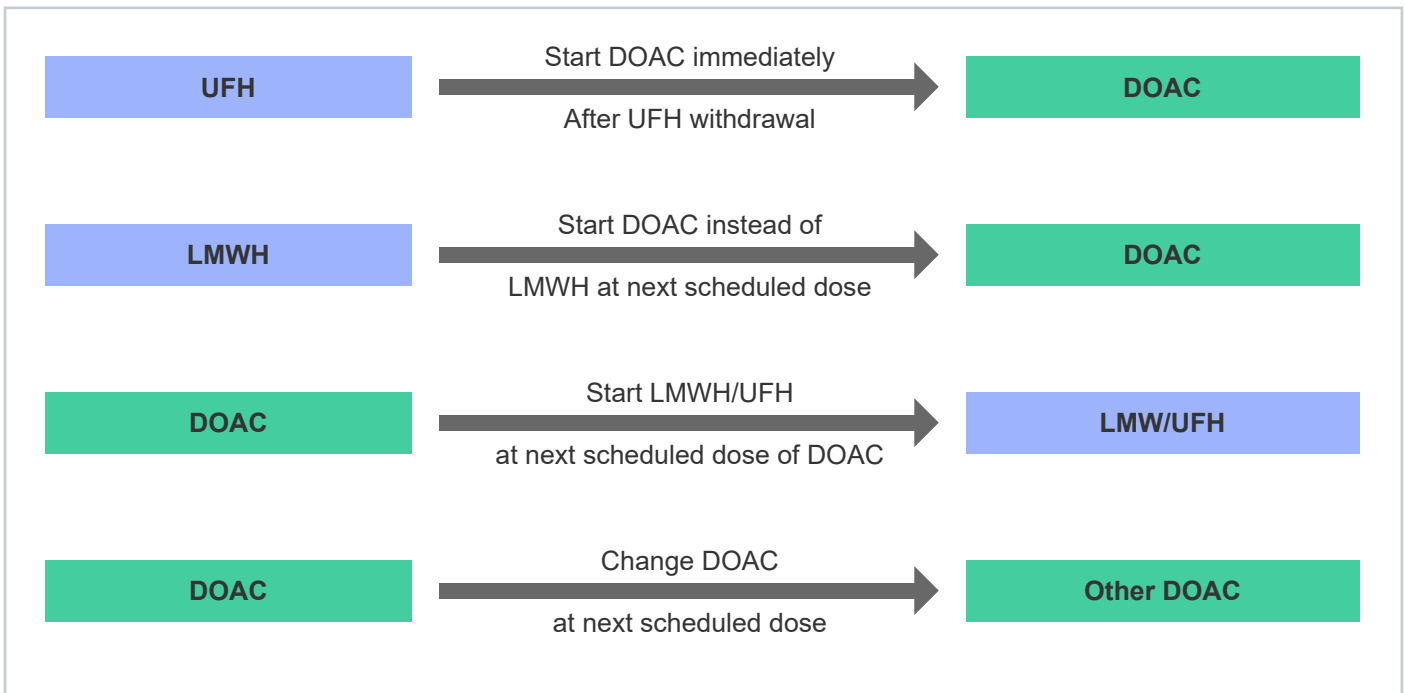
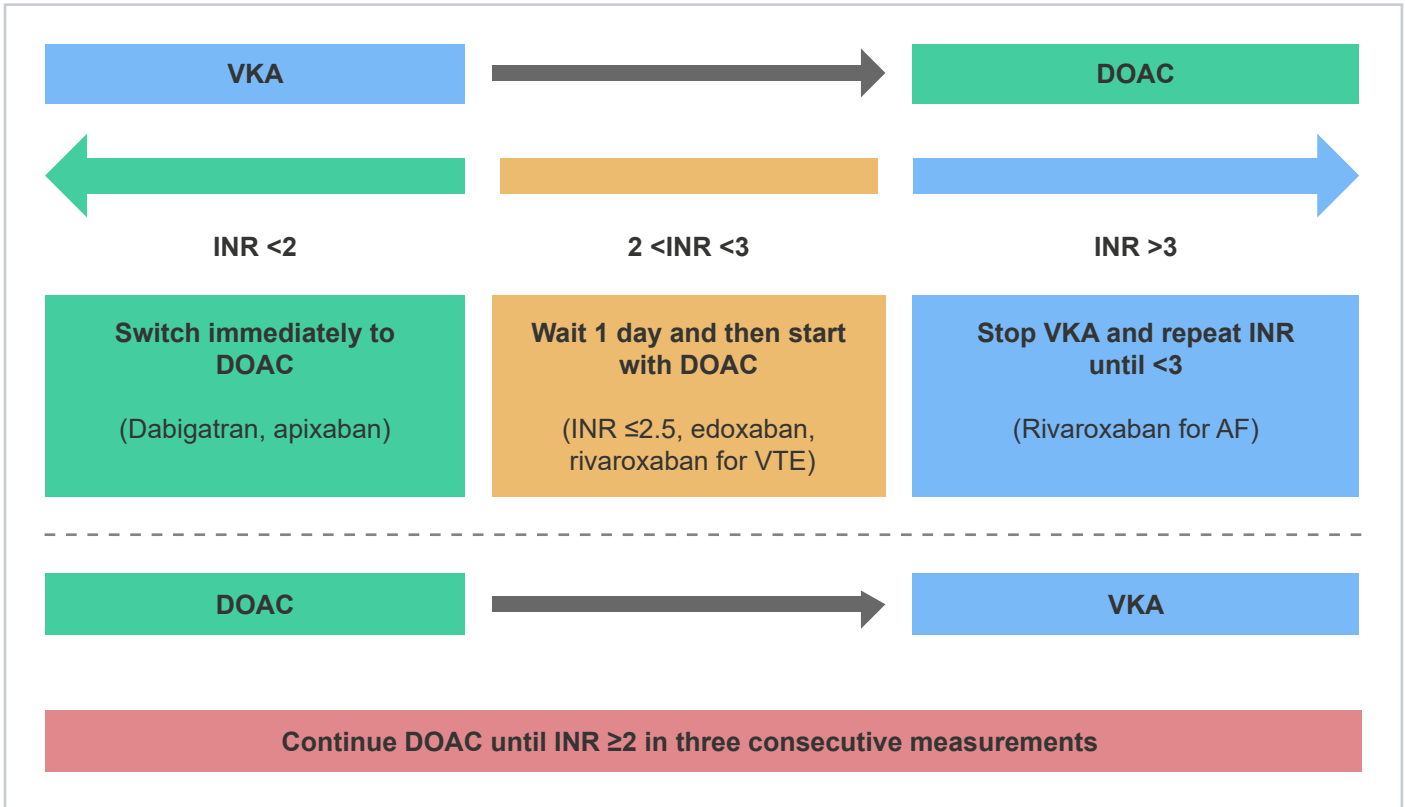
<sup>a</sup> Dosing depends on when and what was the last dose of DOAC; **high dose**: initial IV bolus 800 mg; target infusion rate of 30 mg/min, follow-on IV infusion at 8 mg/min for up to 120 min, **low dose**: initial IV bolus 400 mg; target infusion rate of 30 mg/min, follow-on IV infusion at 4 mg/min for up to 120 min. **Use high dose with** rivaroxaban  $>10$  mg or dose unknown, or apixaban  $>5$  mg or dose unknown, both if dose was received  $<8$  hours or unknown. **Use low dose with** rivaroxaban  $\leq 10$  mg (any timing from last dose), apixaban  $\leq 5$  mg (any timing from last dose), rivaroxaban  $>10$  mg or dose unknown ( $\geq 8$  hours from last dose), or apixaban  $>5$  mg or dose unknown ( $\geq 8$  hours from last dose).

<sup>b</sup> 5 g (administered as 2 separate 2.5 g doses no more than 15 minutes apart). Note: Repeat dosing is not usually required. However, another dose may be considered (despite limited data) if bleeding continues and there is laboratory evidence of persistent dabigatran effect or before an emergent invasive procedure if there is concern for a persistent anticoagulant effect.

Source: 2018 EHRA Practical Guide on NOACs in AF



## Pathway V: Transitioning Between Anticoagulants




Source: Front Cardiovasc Med. 2019;6:17.



01	Chen A, Stecker E, A. Warden B. Direct oral anticoagulant use: A practical guide to common clinical challenges. <i>Journal of the American Heart Association</i> 2020; 9:e017559.
02	Dailymed.nlm.nih.gov. 2020. Dailymed. [Internet] [Cited 25 November 2020]. Available at: < <a href="https://dailymed.nlm.nih.gov/dailymed/">https://dailymed.nlm.nih.gov/dailymed/</a> >
03	Docplayer.net. 2020. [Internet] [Cited 8 December 2020]. Available at: < <a href="https://docplayer.net/">https://docplayer.net/</a> >
04	Doherty JU, Gluckman TJ, Hucker WJ, Januzzi JL, Ortel TL, Saxonhouse SJ, et al. 2017 ACC expert consensus decision pathway for periprocedural management of anticoagulation in patients with nonvalvular atrial fibrillation: A report of the American College of Cardiology Clinical Expert Consensus Document Task Force. <i>Journal of the American College of Cardiology</i> 2017; 69:871–98.
05	Drugs.com. 2020. [Internet] [Cited 8 December 2020]. Available at: < <a href="https://www.drugs.com/">https://www.drugs.com/</a> >
06	January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. <i>Journal of the American College of Cardiology</i> 2014; 64(21):e1–76.
07	January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration with the Society of Thoracic Surgeons. <i>Circulation</i> 2019; 140:e125–51.
08	Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. <i>Chest</i> 2016; 149:315–52.
09	Kristiansen A, Brandt L, Agoritsas T, Akl EA, Berge E, Bondi J, Dahm AE, et al. Adaptation of trustworthy guidelines developed using the GRADE methodology: A novel five-step process. <i>Chest</i> 2014; 146:727–34.
10	Magonlinelibrary.com. 2020. [Internet] [Cited 8 December 2020]. Available at: < <a href="https://www.magonlinelibrary.com/">https://www.magonlinelibrary.com/</a> >
11	Medicines.org.uk. 2020. Home - Electronic Medicines Compendium (Emc). [Internet] [Cited 25 November 2020]. Available at: < <a href="https://www.medicines.org.uk/emc#gref">https://www.medicines.org.uk/emc#gref</a> >
12	Qamar A, Vaduganathan M, Greenberger NJ, Giugliano RP. Oral anticoagulation in patients with liver disease. <i>Journal of the American College of Cardiology</i> 2018; 71:2162–75.
13	Seiffge DJ, Polymeris AA, Fladt J, Lyrer PA, Engelter ST, De Marchis GM. Management of patients with stroke treated with direct oral anticoagulants. <i>Journal of Neurology</i> 2018; 265:3022–33.
14	Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. <i>European Heart Journal</i> 2018; 39:1330–93.
15	UpToDate.com. 2020. [Internet] [Cited 8 December 2020]. Available at: < <a href="https://www.uptodate.com/home">https://www.uptodate.com/home</a> >



 **Table I: CHA2DS2-VASc Score**  
A clinical prediction tool to estimate the risk of stroke in patients with nonvalvular atrial fibrillation

CHA2DS2-VASc Acronym	Points
Congestive heart failure	1 point
Hypertension	1 point
Age >75 years	2 point
Diabetes mellitus	1 point
Stroke/TIA/TE	2 point
Vascular disease (prior MI, PAD, aortic plaque)	1 point
Sex category (i.e. Female sex)	1 point

CHA2DS2-VASc Score	Stroke Rate/Year
0	0
1	1.3%
2	2.2%
3	3.2%
4	4.0%
5	6.7%
6	9.8%
7	9.6%
8	6.7%
9	15.2%



**Table II: HAS-BLED Score**  
Bleeding risk score to quantify the 1-year risk for major bleeding in patients with atrial fibrillation

HAS-BLED Acronym	Points
Hypertension (SBP >160 mmHg)	1 point
Abnormal liver or renal function (1 point each)	1 or 2 points
Stroke History	1 point
Bleeding History	1 point
Labile INRs	1 point
Elderly (>65 years old)	1 point
Drugs that promote bleeding or alcohol (1 point each)	1 or 2 points

HAS-BLED Score	Bleeds per 100 patient years
0	1.13%
1	1.02%
2	1.88%
3	3.75%
4	8.70%
5	12.5%
6	Scores >5 were too rare to determine risk in validation studies
7	
8	
9	



### Table III: Child-Pugh Score for Classification of Hepatic Impairment

Score	1	2	3
Bilirubin	<2 mg/dL (<34.2 mcmol/L)	2 to 3 mg/dL (34.2 to 51.3 mcmol/L)	>3 mg/dL (>51.3 mcmol/L)
Albumin	>3.5 g/dL (35 g/L)	2.8 to 3.5 g/dL (28 to 35 g/L)	<2.8 g/dL (<28 g/L)
Ascites	Absent	Mild	Moderate
Encephalopathy	None	Grade 1 to 2	Grade 3 to 4
INR	<1.7	1.7 to 2.3	>2.3

Grade A, <7 points; Grade B, 7 to 9 points; Grade C, 10 to 15 points